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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,048	02/04/2004	John G. Babish	068911-0062	4840

7590 11/14/2005

Cathryn Campbell
McDERMOTT, WILL & EMERY
Suite 700
4370 La Jolla Village Drive
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EXAMINER	
MELLER, MICHAEL V	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 11/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

DOCKETED

RESPONSE TO NON FINAL OFFICE ACTION
DUE DATE 2/14/06
BAR DATE 5/14/06

jm

Office Action Summary	Application No.	Applicant(s)	
	10/774,048	BABISH ET AL.	
	Examiner	Art Unit	
	Michael V. Meller	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *17-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16, drawn to a composition, classified in class 424, subclass various.

II. Claims 17-32, drawn to a first method of using said composition, classified in class 435, subclass various.

III. Claim 33, drawn to a second method of using said composition, classified in class 530, subclass various.

IV. Claims 34-36, drawn to a third method of using said composition, classified in class 514, subclass various.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can

be used in materially distinct process such as evidenced by the different uses in the claims themselves.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in materially distinct process such as evidenced by the different uses in the claims themselves.

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in materially distinct process such as evidenced by the different uses in the claims themselves.

The different processes are restrictable from eachother since as evidenced by the claims themselves they require have differents effects, uses and modes of operation.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

This application contains claims directed to the following patentably distinct species of the claimed invention: the many different non-aspirin, non-steroidal compounds.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 17, 33, 34 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims

are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Simona Levi-Mintz on 10/18/2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-16 and naproxen. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/44623 (abstract, page 4, lines 3-15, page 6, lines 6-20).

WO teaches that hops and naproxen can be in the same composition. It would have been obvious to select them from the list since they are both noted to be used in a single composition to treat inflammation.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 406312924 (abstract) or JP 04202138 (abstract) taken with Sunshine et al. (US patent No. 4780463-see col. 4, line 65- col. 5, line 15, col. 6, lines 1-20, col. 10, lines 20-30) or CA 2175091 (abstract).

JP 406312924 (abstract) or JP 04202138 (abstract) both teach hops extracts used to treat inflammation.

Sunshine et al. (US patent No. 4780463-see col. 4, line 65- col. 5, line 15, col. 6, lines 1-20, col. 10, lines 20-30) or CA 2175091 (abstract) both teach naproxen used to treat inflammation.

It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Sussman,* 1943 C.D. 518; *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

> The reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention.
>
> MPEP 2144 Sources of Rationale Supporting a Rejection Under 35 U.S.C. 103. <http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2144.htm>

Thus, it would have been obvious to combine the hops with the naproxen in a single composition since naproxen and hops are both known in the art individually to treat inflammation, i.e. to be used as an anti-inflammatory.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael V. Meller whose telephone number is 571-272-0967. The examiner can normally be reached on Monday thru Thursday: 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael V. Meller
Primary Examiner
Art Unit 1655

MVM

Notice of References Cited	Application/Control No. 10/774,048	Applicant(s)/Patent Under Reexamination BABISH ET AL.	
	Examiner Michael V. Meller	Art Unit 1655	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-4,780,463	10-1988	Sunshine et al.	514/226.5
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	CA 2175091	10-1997	Canada	----------	----------
	O	JP 04202138	07-1992	Japan	----------	----------
	P	JP 406312924	11-1994	Japan.	----------	----------
	Q	WO 99/44623	9/1999	PCT	----------	----------
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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L46: Entry 601 of 614 File: DWPI Oct 27, 1997

DERWENT-ACC-NO: 1998-231205
DERWENT-WEEK: 199912

TITLE: Controlled release naproxen tablets - contain 3% hydroxypropyl-methylcellulose and optionally lubricant

INVENTOR: SHERMAN, B C

PATENT-ASSIGNEE:

ASSIGNEE	CODE
SHERMAN B C	SHERI

PRIORITY-DATA: 1996CA-2175091 (April 26, 1996)

Search Selected Search ALL Clear

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CA 2175091 A	October 27, 1997	E	011	A61K031/19
CA 2175091 C	January 5, 1999		000	A61K031/19

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
CA 2175091A	April 26, 1996	1996CA-2175091	
CA 2175091C	April 26, 1996	1996CA-2175091	

INT-CL (IPC): A61 K 9/22; A61 K 31/19; A61 K 47/38

ABSTRACTED-PUB-NO: CA 2175091A
BASIC-ABSTRACT:

A controlled release tablet for once-daily oral administration of naproxen comprises 3% hydroxypropylmethylcellulose (HPMC) with average molecular weight of 190000.

The composition preferably also contains 0.1 to 3% of a lubricant.

USE - Naproxen is a widely used antiinflammatory drug with analgesic and antipyretic properties and is used in the treatment of e.g. arthritis and dysmenorrhea.

ADVANTAGE - Controlled release formulations give better patient compliance and reduced fluctuation of plasma drug concentration. The tables have suitable drug release rate and hardness and only contain 3% expensive HPMC.

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L9: Entry 7 of 7 File: DWPI Jul 22, 1992

DERWENT-ACC-NO: 1992-295331
DERWENT-WEEK: 199718

TITLE: Hop extract for active oxygen scavenger - obtd. from ground humulus lupulus, for malignant rheumatoid arthritis, burns and skin disease treatment

PATENT-ASSIGNEE:

ASSIGNEE	CODE
ASAHI BREWERIES LTD	ASAK

PRIORITY-DATA: 1990JP-0329799 (November 30, 1990)

Search Selected Search ALL Clear

PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	JP 04202138 A	July 22, 1992		006	A61K035/78
☐	JP 2514860 B2	July 10, 1996		005	A61K035/78

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP 04202138A	November 30, 1990	1990JP-0329799	
JP 2514860B2	November 30, 1990	1990JP-0329799	
JP 2514860B2		JP 4202138	Previous Publ.

INT-CL (IPC): A23K 1/30; A23L 1/30; A61K 7/00; A61K 35/78

ABSTRACTED-PUB-NO: JP 04202138A
BASIC-ABSTRACT:

Extract prepd. by extracting ground Humulus lupulus with one or two solvents, and concentrating and drying extract, has active oxygen scavenger action. Main ingredient of extract is lupuronic acid (beta acid), coluprone and adolupurone. Pref. solvent is hexane, ethyl acetate or oil. Prepn. comprises grinding 20 g of hop pellets, adding 400 ml of ethanol, extracting on reflux heating for 1 hr., concentrating to give dark-brown semisolid of 8.2 g, distribution extracting with 160 ml of hexane and 160 ml of water, extracting aq. phase twice with 160 ml of hexane, and condensing extract from hexane phase.

USE/ADVANTAGE - Used as pharmaceuticals, food and cosmeticsrow

CHOSEN-DRAWING: Dwg.0/0

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L9: Entry 6 of 7 File: JPAB Nov 8, 1994

PUB-NO: JP406312924A
DOCUMENT-IDENTIFIER: JP 06312924 A
TITLE: UTILIZATION OF HUMULONES HAVING ANTIOXIDANT ACTION

PUBN-DATE: November 8, 1994

INVENTOR-INFORMATION:

NAME	COUNTRY
TAGASHIRA, MOTOYUKI	

ASSIGNEE-INFORMATION:

NAME	COUNTRY
ASAHI BREWERIES LTD	

APPL-NO: JP05123142
APPL-DATE: April 28, 1993

INT-CL (IPC): A61K 31/12; A61K 31/12; A23L 3/3499; A61K 7/00; A61K 7/48; C09K 15/08

ABSTRACT:

PURPOSE: To provide pharmaceuticals, foods, drinks and cosmetics having antioxidant action and containing, as active components, humulones or their salts constituting the main component of a hop soft resin producible from hop used as a raw material for beer.

CONSTITUTION: The pharmaceuticals, foods, drinks or cosmetics having antioxidant action contain one or more kinds of humulones of formula [R is CH(CH3)2 (cohumulone), CH2CH(CH3)2 (humulone) or CH (CH3)CH2CH2 (adhumulone)] as active components. Humulones are obtained in the form of cohumulone, humulone or adhumulone or their proper mixture from natural hop using Wollmer's method and optionally using a high-performance liquid chromatography. Humulone having antioxidant action acts as a treating agent for adult diseases, malignant rheumatoid arthritis, lesion such as scald, acne, spot, etc., or an antioxidant or degradation preventing agent for foods and drinks.

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 35/78, 31/16, 31/19, 31/60, 31/165 // (A61K 35/78, 31:60) (A61K 35/78, 31:165) (A61K 35/78, 31:19) (A61K 31/19, 31:165) (A61K 31/60, 31:19) (A61K 31/60, 31:165)

A1

(11) International Publication Number: **WO 99/44623**

(43) International Publication Date: 10 September 1999 (10.09.99)

(21) International Application Number: PCT/US99/04786

(22) International Filing Date: 4 March 1999 (04.03.99)

(30) Priority Data:
60/076,737 4 March 1998 (04.03.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/076,737 (CIP)
Filed on 4 March 1998 (04.03.98)

(71) Applicant *(for all designated States except US)*: NPS PHARMACEUTICALS, INC. [US/US]; Suite 240, 420 Chipeta Way, Salt Lake City, UT 84108-1256 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ARTMAN, Linda, D. [US/US]; 2510 East Skyline Drive, Salt Lake City, UT 84108 (US). BALANDRIN, Manuel, F. [US/US]; 9184 South Winter Wren Drive, Sandy, UT 84093 (US).

(74) Agents: BENT, Stephen, A. *et al.*; Foley & Lardner, Suite 500, 3000 K Street, N.W., Washington, DC 20007-5109 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITIONS COMPRISING VALERIAN EXTRACTS, ISOVALERIC ACID OR DERIVATIVES THEREOF WITH A NSAID

(57) Abstract

Preparations and extracts of valerian, as well as isovaleramide, isovaleric acid, and its pharmaceutically acceptable salts, esters, and substituted amides, and other valerian-related compounds, in combination with NSAIDs exhibit clinically significant pharmacological properties which implicate a treatment for acute muscular aches, strains, and sprains which occur from a localized, external insult to a particular muscle or muscle group outside of, or peripheral to, the CNS. The compositions in question generally are non-cytotoxic and do not elicit weakness or sedative activity at doses that are effective for the symptomatic treatment of such pathological conditions.

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COMPOSITIONS COMPRISING VALERIAN EXTRACTS, ISOVALERIC ACID OR DERIVATIVES THEREOF WITH A NSAID

BACKGROUND OF THE INVENTION

The present invention relates to the novel combination therapy of valerian-related products and valerian extracts in combination together with anti-inflammatory agents such as the non-steroidal anti-inflammatory drugs (NSAIDs) to elicit greater, improved relief from pain and muscle tension due to stress or injury. More particularly, the invention provides therapeutic combinations of isovaleramide, isovaleric acid, and/or related compounds with NSAIDs, such as ibuprofen, and methods for using these combinations for treating patients suffering from acute lower back pain.

Many agents currently employed in the treatment of muscle pain, such as lower back pain, reduce inflammation, yet provide no decrease in muscle tone, which is a significant component of acute muscle pain. Likewise, many of the currently employed agents that elicit a decrease in muscle tone, for example, benzodiazepines, do not reduce inflammation.

It is apparent, therefore, that compositions that can both reduce inflammation and elicit a decrease in muscle tone are greatly to be desired. It also is apparent that improved methods for treating pain and muscle tension are highly desirable.

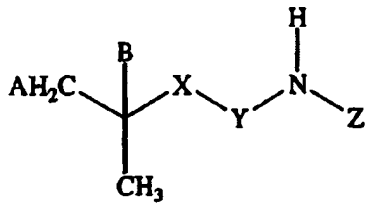
SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a therapeutic combination of valerian extract and/or valerian-related compounds together with at least one NSAID for the improved relief from pain and muscle tension due to stress or injury.

It also is an object of the present invention to provide a method for alleviating one or more symptoms associated with acute muscle pain that is ameliorated by means of a decrease in muscle tone.

It is another object of the present invention to provide a novel combination therapy for the treatment of treating a pathology that is ameliorated by a decrease in muscle tone and a reduction in inflammation.

In accomplishing these and other objectives, there has been provided, according to one aspect of the present invention, the use of a combination of: (a) at least one non-steroidal anti-inflammatory compound, and; (b) at least one compound selected from the group consisting of isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, a pharmaceutically acceptable amide of isovaleric acid and a compound having the structure:



where A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2

and where the compound is selected from the group consisting of 2-methyl isovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate, in the preparation of a pharmaceutical formulation for use in a method of treating a pathology that is ameliorated by a

decrease in muscle tone and a reduction in inflammation, whereby at least one symptom of that pathology is alleviated.

In accordance with another aspect of the invention, the pathology is selected from the group consisting of acute muscular aches, strains, and sprains which occur from a localized, external insult to a particular muscle or muscle group outside of, or peripheral to, the CNS. In one embodiment, the pathology is lower back pain, and in another embodiment, the pathology is ameliorated by a decrease in inflammation, pain, and muscle tone.

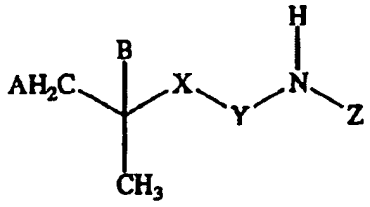
In accordance with yet another aspect of the invention, the non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, a non-steroidal antiinflammatory acetic acid, a fenamate, an oxicam, and a non-steroidal anti-inflammatory propionic acid. In one embodiment, the non-steroidal anti-inflammatory compound is selected from the group consisting of sodium salicylate, acetaminophen, phenacetin, ibuprofen, ketoprofen, indomethacin, flurbiprofen, diclofenac, naproxen, piroxicam, tebufelone, etodolac, nabumetone, tenidap, alcofenac, antipyrine, amimopyrine, dipyrone, animopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafenine, flufenamic acid, glaphenine, indoprofen, meclofenamic acid, mefenamic acid, niflumic acid, salidifamides, sulindac, suprofen, tolmetin, nabumetone, tiaramide, proquazone, bufexamac, flumizole, tinoridine, timegadine, dapsone, diflunisal, benorylate, fosfosal, fenclofenac, etodolac, fentiazac, tilomisole, carprofen, fenbufen, oxaprozin, tiaprofenic acid, pirprofen, feprazone, piroxicam, sudoxicam, isoxicam, celecoxib, Vioxx® and tenoxicam. In another embodiment, the non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, sodium salicylate, acetaminophen, ibuprofen, ketoprofen, and naproxen.

In accordance with still another aspect of the invention, the composition comprises a pharmaceutically acceptable amide of isovaleric acid, where the amide is isovaleramide. In preferred embodiments, the composition comprises

isovaleramide together with ibuprofen, aspirin, acetaminophen, acetylsalicylic acid, naproxen, or ketoprofen.

In accordance with a still further aspect of the invention there has been provided a use of an extract of Valerianaceae, cramp bark, black haw, or hops in combination with at least one non-steroidal anti-inflammatory compound in the preparation of a pharmaceutical formulation for use in a method of treating acute muscular aches, strains, and sprains which occur from a localized, external insult to a particular muscle or muscle group outside of, or peripheral to, the CNS wherein the extract comprises at least one compound that is hydrolyzed *in vivo* to yield isovaleric acid or isovaleramide. In particular embodiments the non-steroidal anti-inflammatory compound is ibuprofen, aspirin, acetaminophen, acetylsalicylic acid, naproxen, or ketoprofen.

In accordance with yet another aspect of the invention there has been provided a pharmaceutical composition comprising (a) at least one non-steroidal anti-inflammatory compound, and; (b) at least one compound selected from the group consisting of isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, a pharmaceutically acceptable amide of isovaleric acid and a compound having the structure:



where A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2

and where that compound is selected from the group consisting of 2-methyl isovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate, together with a pharmaceutically acceptable diluent, excipient, or carrier.

In one embodiment, the non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, a non-steroidal antiinflammatory acetic acid, a fenamate, an oxicam, and a non-steroidal anti-inflammatory propionic acid. In another embodiment, the non-steroidal anti-inflammatory compound is selected from the group consisting of sodium salicylate, acetaminophen, phenacetin, ibuprofen, ketoprofen, indomethacin, flurbiprofen, diclofenac, naproxen, piroxicam, tebufelone, etodolac, nabumetone, tenidap, alcofenac, antipyrine, amimopyrine, dipyrone, animopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafenini, flufenamic acid, glaphenine, indoprofen, meclofenamic acid, mefenamic acid, niflumic acid, salidifamides, sulindac, suprofen, tolmetin, nabumetone, tiaramide, proquazone, bufexamac, flumizole, tinoridine, timegadine, dapsone, diflunisal, benorylate, fosfosal, fenclofenac, etodolac, fentiazac, tilomisole, carprofen, fenbufen, oxaprozin, tiaprofenic acid, pirprofen, feprazone, piroxicam, sudoxicam, isoxicam, celecoxib, Vioxx© and tenoxicam. In yet another embodiment, the non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, sodium salicylate, acetaminophen, ibuprofen, ketoprofen, and naproxen.

In a particular embodiment, the composition comprises a pharmaceutically acceptable amide of isovaleric acid, where that amide is isovaleramide. In other embodiments, the composition comprises isovaleramide together with aspirin, sodium salicylate, acetaminophen, ibuprofen, ketoprofen, or naproxen.

In accordance with a still further aspect of the invention, there has been provided a pharmaceutical composition comprising an extract of Valerianaceae, cramp bark, black haw, or hops and at least one non-steroidal anti-inflammatory compound, together with a pharmaceutically acceptable diluent, excipient, or carrier. In particular embodiments the non-steroidal anti-inflammatory compound is aspirin, sodium salicylate, acetaminophen, ibuprofen, ketoprofen, or naproxen.

Other objects, features, and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the present invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the structures of isovaleramide and various structurally-related compounds, including isovaleramide.

Figure 2 depicts the structures of additional compounds that are structurally related to isovaleramide.

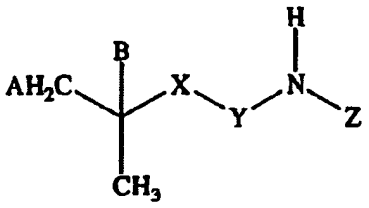
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Valerian extracts and valerian-related compounds can be administered in combination with at least one NSAID compound, such as ibuprofen, *in vivo* to reduce acute muscle pain by decreasing muscle tone and inflammation. That is,

this combination therapy surprisingly provides greatly improved relief of muscle inflammation and tone as compared to administration of either NSAIDs or valerian-related compounds and extracts alone.

The valerian extracts that are suitable for use in the invention are those extracts that, upon hydrolytic or metabolic breakdown *in vivo*, release isovaleric acid, isovaleramide, or a related compound. These extracts may be used in combination with at least one NSAID. The extracts may be coadministered with the NSAID(s), or may be formulated into a pharmaceutical composition with the NSAID(s) so that the extract and the NSAID(s) are delivered to the patient essentially simultaneously. The skilled artisan also will recognize that the present invention also comprehends the use of compositions containing (i): (a) combinations of valerian extracts with valerian-related compounds such as isovaleramide, together with (b) one or more NSAID compounds; and (ii) (a) a single valerian extract or valerian-related compound, together with (b) one or more NSAID compounds.

In the context of the present invention, a valerian-related compound is a compound selected from the group consisting of isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, isovaleramide, or another pharmaceutically acceptable amide of isovaleric acid, and a compound having the structure



where A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2

The structures of these compounds are shown in Figures 1 and 2 and include substituted isovaleramides such as 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, and 2,2-dimethyl-n-butyramide. The valerian-related compounds also include certain sulfonamide, sulfamate, and carbamate compounds that, by virtue of their structural similarity to isovaleramide, share similar pharmacological activities. Preferred sulfonamides and sulfamates include 2-methyl-1-propylsulfonamide, 1-methylethyl sulfamate, and 2-methyl-1-propyl sulfamate. Preferred carbamates include isobutylcarbamate ($(CH_3)_2CHCH_2OCONH_2$) and isopropylcarbamate ($(CH_3)_2CHOCONH_2$).

For each of these compounds that contains one or more asymmetric centers, the present invention specifically includes each of the possible enantiomeric or diastereomeric forms of the compound. The nature of the valerian-related compounds and the NSAID compounds are discussed in more detail below.

In the context of the present invention, compounds are said to be "coadministered" to a patient when the compounds are administered at times that are sufficiently close together that the compounds are pharmacologically active and present in a pharmaceutically effective concentration in the patient at the same time. For example, a valerian extract may be administered to a patient some time after administration of an NSAID, but is considered to be coadministered with the NSAID if the NSAID is still present in a pharmaceutically effective concentration in the patient.

Methods For Preparing Pharmaceutical Formulations

Preparation of active compounds

The rhizomes and roots of *Valeriana* spp. (common name: valerian; family Valerianaceae) have been used for medicinal purposes since ancient times. The most commonly used valerian preparations include aqueous and hydroalcoholic extracts, such as tinctures, intended for oral administration. In addition, ammoniated valerian tinctures were used medicinally in the English-speaking world since at least the beginning of the seventeenth century. Hobbs, *HerbalGram* No. 21: 19-34 (1989). In the last three decades, the sedative and antispasmodic properties of valerian preparations have been attributed primarily to the presence of chemically labile monoterpenoid iridoid triester compounds called valepotriates ("valerian-epoxy-triesters (-ates)").

The most common and abundant of the valepotriates, valtrate and didrovaltrate, each contain two isovalerate moieties esterified to a "central" iridoid nucleus. Lin *et al.*, *Pharm. Res.* 8: 1094-1102 (1991). However, these acid- and heat-labile substances do not survive intact in the stomach following oral administration, and readily release two moles of isovaleric acid for every mole of valepotriate. Furthermore, aqueous extracts of valerian rhizomes and roots retain their biological properties, even though the valepotriate triesters are water-insoluble. Bos *et al.*, *Phytochem. Anal.* 7: 143-51 (1996).

The major, water-soluble, active principle of commonly used valerian extracts and other preparations, such as aqueous or hydroalcoholic extracts or tinctures, has been determined to be the ester hydrolysis product, isovaleric acid. Ammonium isovalerate and isovaleramide are produced in ammoniated tinctures. Balandrin *et al.*, *J. Toxicol.-Toxin Rev.* 14: 165 (1995). The structures of isovaleramide and structurally-related compounds are depicted in Figures 1 and 2. In this way, the chemically labile valepotriates and other valerian-derived monoterpenoid-isovalerate esters, such as bornyl and lavandulyl isovalerates, act as "pro-drugs" and chemical precursors for isovaleric acid, its salts, and isovaleramide.

Isovaleramide has been isolated from valerian plants, most probably as an isolation artifact following treatment with ammonia. Buckova *et al.*, *Cesk. Farm. 26*: 308 (1977); *Chem. Abstr. 88*: 86063z (1978); see also Bos *et al.* and Fuzzati *et al.*, *Phytochem. Anal.* 7: 143, 76 (1996). More recently, isovaleramide was shown to exhibit low acute toxicity *in vivo*, no mutagenic potential, and clinically useful anxiolytic properties. U.S. patent No. 5,506,268; PCT application WO 94/28,888. Methods for preparing isovaleramide are well known.

Extracts of medicinal plants that are useful for treating the symptoms of muscle (or muscular) tension can be prepared by aqueous, hydroalcoholic, or alcoholic extraction, or by extraction with other suitable solvents using methods well known to those of skill in the art. In the context of the present invention, useful extracts contain at least one of the following: isovaleric acid, its salts or complexes, ethyl isovalerate, isovaleramide, *N*-ethyl isovaleramide, and their chemical precursors. Useful extracts also share the common property of releasing isovaleric acid and/or isovaleramide upon hydrolysis *in vivo*. Standard methods for preparing such extracts can be found in pre-1950 editions of the U.S. PHARMACOPOEIA (U.S.P.) and the NATIONAL FORMULARY (N.F.), as well as in well-known references such as Gennaro (Ed.), REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ed. (Mack Publishing Co. 1990), Tyler *et al.*, PHARMACOGNOSY, 9th ed. (Lea and Febiger 1988), and Hare *et al.*, THE NATIONAL STANDARD DISPENSATORY (Lea Brothers 1905). Additional citations appear in U.S. patent No. 5,506,268 and PCT application WO 94/28,888, which are hereby incorporated by reference in their entirety.

The principal historic sources of naturally occurring isovaleric acid have been valerian rhizomes and roots, as well as those of closely related plants in the family Valerianaceae. As discussed by Hobbs (1989), *supra*, these include the common valerian plant, *Valeriana officinalis* L., as well as the East Indian valerian, *V. wallichii* DC., and the biblical spikenard, *Nardostachys jatamansi*

(Roxb.) DC. In addition to valerian rhizomes and roots, other plants which have been used traditionally as sedative or "antispasmodic" herbal medicines are known to contain, or to produce, isovaleric acid. These include hops (*Humulus lupulus* L., family Moraceae, which is often used in herbal formulations in combination with valerian), "cramp bark" or "guelder rose" (*Viburnum opulus* L., family Caprifoliaceae), and "black haw" (*V. prunifolium* L., root bark). Hare *et al.*, THE NATIONAL STANDARD DISPENSATORY, pages 93, 94, 159, 160, 169, 256, 642, 692-694, 766, 767, 932, 1031, 1383, 1384, 1426, 1479, 1480, 1571, 1572, 1619, 1620, 1631-1633, 1661, and 1662 (Lea Brothers 1905); Heyl *et al.*, *J. Am. Chem. Soc.* 42: 1744 (1920); Grier, *Pharm. J. Pharm.* 68: 302 (1929); Grier, *Chem. Drug. (London)* 110: 420 (1929); Grieve, A MODERN HERBAL, pages 35-40, 265-276, 381, 382, 411-415, 744-746, 781, 782, and 824-830 (Hafner 1959); Holbert, *J. Am. Pharm. Assoc., Sci. Ed.* 35: 315 (1946); Hoffmann, THE HERBAL HANDBOOK: A USER'S GUIDE TO MEDICAL HERBALISM, pages 38, 39, 83 and 84 (Healing Arts Press 1989).

As in the case of valerian rhizomes and roots, hops generate isovaleric acid from more chemically complex precursors upon oxidation or enzymatic breakdown. Millspaugh, AMERICAN MEDICINAL PLANTS, AN ILLUSTRATED AND DESCRIPTIVE GUIDE TO THE AMERICAN PLANTS USED AS HOMEOPATHIC REMEDIES, pages 622-626 (Dover 1974); Hare *et al.*, THE NATIONAL STANDARD DISPENSATORY, pages 766-767 (Lea Brothers 1905); Grier, *Chem. Drug. (London)* 110: 420 (1929); Grieve, A MODERN HERBAL, pages 411-415 (Hafner 1959); Stevens, *Chem. Rev.* 67: 19 (1967); Duke, CRC HANDBOOK OF MEDICINAL HERBS, page 557 (CRC Press 1985).

Pharmaceutically acceptable salts of organic acids, such as isovaleric acid, which have been approved by the U.S. Food and Drug Administration for commercial marketing include sodium, potassium, lithium, zinc, aluminum, calcium, or magnesium salts. REMINGTON'S PHARMACEUTICAL

SCIENCES, 18th ed., page 1445 (Mack Publishing Co. 1990). Salts of isovaleric acid that are commercially available in the United States include the ammonium, sodium, potassium, and zinc isovalerates.

Pharmaceutically acceptable alcohols can form esters with isovaleric acid via the corresponding isovaleric acid chloride and/or anhydride by methods that are well known in the art. See, for example, March, ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS, AND STRUCTURE, fourth ed. (John Wiley and Sons 1992). Such alcohols contain one or more hydroxyl or phenol groups, and are well tolerated *in vivo*. Examples of suitable alcohols include ethanol, certain carbohydrates and related compounds such as glucose, fructose, sucrose, xylose, and lactose, sugar alcohols such as dulcitol, mannitol, and sorbitol, sugar acids such as gluconic and glucuronic acids, glycerol, the polyol inositol, benzyl alcohol, certain phenols such as phenol, salicylic acid, saligenin, salicylamide, vanillin, *p*-hydroxycinnamic acid (*p*-coumaric acid), caffeic acid, ferulic acid, gallic acid, ellagic acid, quercetin, and eugenol. Other examples of suitable alcohols include alkaloids and biogenic amines such as ephedrine, pseudoephedrine, phenylpropanolamine, tyramine, and dopamine, vitamins such as ascorbic acid (vitamin C), thiamine (vitamin B1), riboflavin (vitamin B2), pyridoxine (vitamin B6), cyanocobalamin (vitamin B12), the tocopherols (vitamin E), choline, folic acid, and pantothenic acid, monoterpenoid alcohols such as geraniol, nerol, and linalool, naturally occurring triterpenoid alcohols such as α- and β-amyrins, lupeol, and oleanolic and ursolic acids, bile acids such as cholic acid, deoxycholic acid, and taurocholic acid and common, naturally occurring, plant sterols (phytosterols) such as β-sitosterol, stigmasterol, campesterol, and brassicasterol. Tyler *et al.*, PHARMACOGNOSY, 9th ed. (Lea and Febiger 1988). Other such well-tolerated hydroxyl- and phenol-containing compounds can be readily identified by those skilled in the art by consulting standard reference works such as THE MERCK INDEX and REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ed. (Mack Publishing Co. 1990). Esters of isovaleric acid that are

commercially available in the United States include the bornyl, ethyl, *n*-butyl, isoamyl, and geranyl isovalerates.

Isovaleric acid, ammonium isovalerate, and the esters ethyl isovalerate, isoamyl isovalerate, 2-methylbutyl isovalerate, cinnamyl isovalerate, methyl isovalerate, bornyl isovalerate, isobornyl isovalerate, and menthyl isovalerate, among other isovalerate esters, are listed in the Code of Federal Regulations by the FDA as being acceptable flavoring agents which may be used in foods. 21 CFR §172.515 (1991). Valerian (*Valeriana officinalis* L.) rhizomes and roots and black haw (*Viburnum prunifolium* L.) bark are listed as acceptable natural flavoring substances and natural adjuvants in 21 CFR §172.510 (1991). Hops and "lupulin" are listed among substances that are generally recognized as safe ("GRAS"). 21 CFR §182.20 (1991).

Generally, esters of isovaleric acid are expected to be hydrolyzed *in vivo* by ubiquitous esterase enzymes, thereby releasing isovaleric acid and the constituent alcohol or phenol. Particularly preferred among the isovalerate esters are glyceryl mono-, di-, and especially tri-isovalerates ("triisovalerin"), isovaleryl salicylic acid or salicylate (salicylic acid isovalerate), ethyl isovalerate, and β-sitosteryl isovalerate. See Figure 1. Hydrolysis of these isovalerate esters *in vivo* releases isovaleric acid and glycerol (glycerin), salicylic acid (an analgesic, anti-inflammatory, and febrifuge), ethanol (ethyl alcohol or common "alcohol," a CNS depressant), and β-sitosterol (a harmless phytosterol), respectively. With the exception of ethyl isovalerate, these esters are non-volatile or only slightly volatile, thereby minimizing any unpleasant odors. Furthermore, in pure form these esters possess the advantage of having neutral to pleasant odors, in contrast to the extremely unpleasant odors of isovaleric acid and its salts, such as the ammonium, sodium, potassium, and zinc isovalerate salts. Moreover, whereas ethyl isovalerate is a liquid, the glyceryl mono-, di-, and tri-isovalerates, isovaleryl salicylate, and β-sitosteryl isovalerate are expected to be solids at room temperature, thereby facilitating their formulation into various standard solid and liquid oral dosage forms well

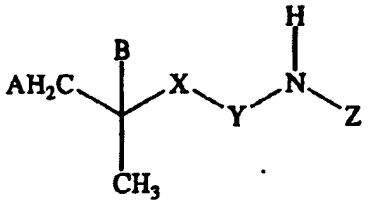
known in the art, such as tablets (*e.g.*, uncoated tablets, enteric-coated tablets, and film-coated tablets), capsules, gelcaps, powders, concentrates (drops), elixirs, tinctures, and syrups.

In addition to isovaleramide, various substituted amides of isovaleric acid can be prepared by methods well known in the art. See, for example, March, ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS, AND STRUCTURE, 4th ed. (John Wiley and Sons 1992). Preferred amides for use in the present invention include *N*-ethyl isovaleramide, *N*-methyl isovaleramide, *N,N*-dimethyl isovaleramide, *N*-methyl,*N*-ethyl isovaleramide, *N*-isovaleryl GABA, *N*-isovaleryl glycine, and N-isovalerylglycinamide. See, for example, Tanaka *et al.*, *J. Biol. Chem.* 242: 2966 (1967). *N,N*-Diethyl isovaleramide ("Valyl"), although purported to possess CNS depressant (sedative) activity, has recently been shown to possess CNS stimulant (convulsant) properties; see U.S. patent No. 5,506,268 and PCT application WO 94/28,888, *supra*. An amide of isovaleric acid with *p*-aminophenol also can be prepared using standard methods to provide a compound, "isovaleraminophen," which is related structurally to the drug acetaminophen (Tylenol®; see Figure 1). In a manner analogous to that of the isovalerate esters, these substituted amides should be hydrolyzed *in vivo* (in this case, via hepatic amidase enzymes), releasing isovaleramide or isovaleric acid.

The compounds and preparations discussed above represent alternative forms for delivering isovaleric acid or isovaleramide *in vivo*. In certain cases, such as with isovaleryl salicylic acid and ethyl isovalerate, the pharmacologically active moiety corresponding to the alcohol or phenol portion may be expected to exert its own pharmacological effects. For example, compounds such as "isovaleraminophen" would be expected to exhibit a "acetaminophen-like" effect, as well as the effect expected from the isovaleric acid or isovaleramide moiety. Such novel chemical combinations of a previously known, pharmacologically active alcohol, phenol, or primary or secondary amine with isovaleric acid fall within the scope of the present

invention. Similar chemical combinations with 2-methylisovaleric acid, 3-methylisovaleric acid, 2,2-dimethylisovaleric acid, 2,3-dimethylisovaleric acid, 4-methylisovaleric acid, 2,4-dimethylisovaleric acid, 3,4-dimethylisovaleric acid, 2,2,4-trimethylisovaleric acid, 3-hydroxyisovaleric acid, 4-hydroxyisovaleric acid, 4-hydroxy-3-methyl-isovaleric acid, 2-hydroxyisovaleric acid, and 2,2-dimethyl-n-butyric acid are within the scope of the present invention.

In addition to isovaleric acid, and its salts, esters and amides discussed above, the present invention also contemplates the use of compounds that are structurally related to isovaleramide. These compounds have the structure:



where A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2,

Preferred compounds having this structure include 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

The valerian-related compounds of the present invention may be prepared using synthetic methods that are well known in the art. For example, many of the carboxylic acid precursors of the amide compounds are commercially available, for example from the Aldrich Chemical Co., Milwaukee, WI, and can be converted into the corresponding amide by preparation of the acid chloride with thionyl chloride or oxalyl chloride, followed by reaction with ammonia or an amine. For compounds containing a hydroxyl group distal to the carboxyl group, the hydroxyl group first is protected using a suitable protecting group as described, for example, in Green, "Protective Groups in Organic Synthesis", Wiley (1981), prior to preparation of the acid chloride. 2-hydroxy and 3-hydroxy isovaleramide are metabolites of isovaleramide *in vivo*, and can be isolated in high yield from the urine of a patient being treated with isovaleramide.

For compounds where the starting acid is not commercially available, the required acid can be prepared by straightforward methods of organic synthesis known to the skilled chemist. For example, carboxylic acid esters may be deprotonated with a strong non-nucleophilic base, such as lithium diisopropylamide, followed by alkylation with methyl iodide or methyl trifluoromethanesulfonate. The alkylated ester is hydrolyzed and converted to the amide by the methods described above.

When the compounds contain one or more asymmetric centers, the individual enantiomers may be prepared from optically active starting materials, or separated by traditional methods of resolution, such as fractional crystallization of salts with chiral amines, or by preparation of amides with chiral amides, chromatographic separation, and hydrolysis of the amides. Alternatively, the amides can be prepared by well known methods of asymmetric synthesis, such as alkylation of an ester or amide of the acid prepared using a chiral auxiliary. See, for example, Evans *et al, Tetrahedron*, 44:5525 (1988) and Fadel *et al. Asymmetry* 1994:531.

The NSAID compounds suitable for use in the present invention are well known in the art. NSAID compounds generally may be divided into sub-classes based upon their structural type, as shown below:

Sub-class	Examples
Acetylsalicylic acid	aspirin
acetic acids	diclofenac indomethacin ketorolac nabumetone sulindac tolmetin
fenamates	meclofenamate mefenamic acid
oxicams	piroxicam
propionic acids	ibuprofen ketoprofen naproxen oxaprozin

Each of these classes of compounds is suitable for use in the present inventions. NSAID compounds that may be used in combination with valerian extracts and/or with the valerian related compounds described above include those described in Chapter 27 of GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th ed., pages 617-657 (McGraw-Hill, 1996), which is hereby incorporated by reference in its entirety.

These compounds include, but are not limited to salicylates, including aspirin, sodium salicylate, acetaminophen, phenacetin, ibuprofen, ketoprofen, indomethacin, flurbiprofen, diclofenac, naproxen, piroxicam, tebufelone, etodolac, nabumetone, tenidap, alcofenac, antipyrine, amimopyrine, dipyrone, animopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole,

fenoprofen, floctafenine, flufenamic acid, glaphenine, indoprofen, meclofenamic acid, mefenamic acid, niflumic acid, salidifamides, sulindac, suprofen, tolmetin, nabumetone, tiaramide, proquazone, bufexamac, flumizole, tinoridine, timegadine, dapsone, diflunisal, benorylate, fosfosal, fenclofenac, etodolac, fentiazac, tilomisole, carprofen, fenbufen, oxaprozin, tiaprofenic acid, pirprofen, feprazone, piroxicam, sudoxicam, isoxicam, celecoxib, Vioxx® and tenoxicam. Each of these compounds is commercially available or may be prepared by methods that are well known in the art.

Preparation of pharmaceutical compositions

The present invention also is directed to pharmaceutical compositions containing combinations of the active compounds described above. The pharmaceutical compositions can contain combinations of two or more of the active compounds. The pharmaceutical formulations of the present invention can be prepared according to known methods, whereby active agents are combined in a mixture with a pharmaceutically acceptable carrier. For instance, see REMINGTON'S PHARMACEUTICAL SCIENCES and GOODMAN AND GILMAN'S, both cited above. A composition is said to be in a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers (e.g. saline and Ringer's solutions) are well known to those skilled in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*.

In general, the dosages of the muscle-tone decreasing agents and the NSAID compounds described herein will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition, and previous medical history. For purposes of therapy, a compound of the present invention and a pharmaceutically acceptable carrier are administered to a subject in need of such treatment in a therapeutically effective amount. The combination of active agent and carrier is said to be administered in a "therapeutically effective

amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient. In the present context, for example, a muscle tone-decreasing agent is physiologically significant if the presence of the agent results in the alleviation of muscle pain.

Isovaleramide and structurally-compounds can be administered orally using solid oral dosage forms such as enteric-coated tablets, caplets, gelcaps, or capsules, or via liquid oral dosage forms such as syrups or elixirs. The indicated dosage of isovaleramide and related compounds as agents that elicit reductions in muscle tone and pain is on the order of 50-1200 mg per dose. Unit solid oral dosage forms preferably contain about 200-600 mg of active ingredient per tablet or capsule, at a dosage of 1-20 mg/kg body weight. Liquid formulations can also be employed with active ingredient compositions so as to provide 1-2 teaspoonfuls per dose. Furthermore, corresponding reduced dosage pediatric chewable and liquid oral dosage forms can also be prepared and administered. These compounds also can be added to foods and beverages in the form of drops (with a dropper from a "concentrate" preparation) for oral administration. In addition, compounds such as isovaleramide may be formulated into chewing gum to facilitate oral delivery and absorption. Appropriate dosages for each of the NSAID compounds used in the present invention are well known in the art.

Alternatively, isovaleramide and related compounds can be administered by injection or other systemic routes, such as transdermal or transmucosal administration, for example, nasally, buccally, or rectally, via suppositories. Oral administration is much more convenient, however, and therefore is preferred.

The present invention thus contemplates a variety of pharmaceutical compositions containing isovaleramide, isovaleric acid, and/or its pharmaceutically acceptable salts, substituted amides, and alcohol esters as active ingredients that are suitable for oral, parenteral, transdermal,

transmucosal, intranasal, buccal, or rectal administration. Although such compounds may be present as incidental by-products in certain pharmaceutical formulations which are outside the scope of the present invention, the common feature of the present formulations is that isovaleramide, isovaleric acid, and/or its pharmaceutically acceptable salts, substituted amides, and alcohol esters are present in a standardized amount. That is, the pharmaceutical formulations contain a predetermined, chemically defined, and quantifiable amount of at least one of such compounds to enable the determination of the quantity of a particular composition required to achieve the dosage levels described herein.

It is further understood that isovaleramide and/or related compounds can be used in combination with other pharmaceutically active ingredients, such as NSAIDs to prepare novel pharmaceutical compositions.

3. DEMONSTRATING THERAPEUTICALLY-RELEVANT ACTIVITY

The suitability and effectiveness of a given pharmaceutical formulation for the alleviation of a pathology, as discussed above, can be demonstrated using case studies such as (but not limited to) those described below.

A commercially prepared extract of valerian (Baldriparan stark N, a preparation from Germany, containing alcohol/water extracts of Baldrian (valerian) Hopfen (hops), and Melissa (lemon balm) in a coated hard-pressed tablet was taken in combination with ibuprofen to obtain improved, greater relief from lower back pain due to undue stress/exercise than the relief that can be obtained with either preparation administered by itself.

Set forth below are two individual case reports from persons using the above combination for relief of pain and muscle tension resulting from injury to the lower back due to exercise or stress. These examples are provided for purposes of illustration and are not intended to be limiting of the invention.

Example 1: Use of a Valerian Preparation and Ibuprofen to Alleviate Pain and Increased Muscle Tone due to Recurrent, Excessive Lower Back Pain.

A male, age 33 years, was complaining of recurrent excessive lower back pain from prior injuries. During a bout of lower back pain, he stated that he could not sleep or sit comfortably and was in duress from the constant pain. He had tried using Doan's Pills and various amounts of ibuprofen, aspirin, or acetaminophen without any useful sense of relief. Likewise, he had tried two of the Baldriparan tablets without any useful sense of relief. It was suggested that he try taking two of the Baldriparan tablets along with 400 mg of ibuprofen. It was stated that the ibuprofen would provide a decrease in inflammation and some analgesic therapy whereas the addition of the valerian and hops extract could provide a decrease in the muscle tone and analgesia as well, thereby allowing for relief from the pain. The next morning, he reported that he took the novel combination of Baldriparan and ibuprofen as suggested before he went to bed. Not only did he sleep well, but he also reported considerable relief from the pain of his back upon awakening. His spouse stated that he "acted like a new man" because he was not grimacing and stooped from pain. He continued to take this combination over the next several days and it continued to provide exceptional relief, without any adverse side effects such as cognition impairment, sedation or withdrawal symptoms.

Example 2: Use of a Valerian Preparation and Ibuprofen to Alleviate Pain and Increased Muscle Tone due to an Acute Muscle Strain from Overexertion

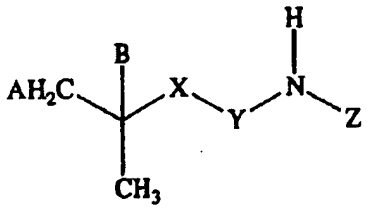
A female, age 23 years, complained of excessive lower back pain that interfered with sleeping and the general activities of daily living such as sitting or standing. She had injured her back while shoveling deep snow from her driveway and sidewalk. She had been taking ibuprofen but experiencing little relief. It was suggested that she take two tablets of the valerian preparation (as stated in the above example) with 400 mg of ibuprofen for the same reasons stated in the first example. The next day she reported that she experienced

significant relief from the pain and requested additional tablets. She also stated that she did not experience any adverse effects from the preparation. She continued to take the combination until her back healed and no longer gave her pain without medication.

5

What Is Claimed Is:

1. The use of a combination of: (a) at least one non-steroidal anti-inflammatory compound, and; (b) at least one compound selected from the group consisting of isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, a pharmaceutically acceptable amide of isovaleric acid and a compound having the structure:



wherein A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2

and wherein said compound is selected from the group consisting of 2-methyl isovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate,

in the preparation of a pharmaceutical formulation for use in a method of treating a pathology that is ameliorated by a decrease in muscle tone and a

reduction in inflammation, whereby at least one symptom of said pathology is alleviated.

2. A use according to claim 1, wherein said pathology is selected from the group consisting of acute muscular aches, strains, and sprains which occur from a localized, external insult to a particular muscle or muscle group outside of, or peripheral to, the CNS.

3. A use according to claim 2, wherein said pathology is lower back pain.

4. A use according to claim 1, wherein said pathology is ameliorated by a decrease in inflammation, pain, and muscle tone.

5. A use according to claim 1, wherein said non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, a non-steroidal antiinflammatory acetic acid, a fenamate, an oxicam, and a non-steroidal anti-inflammatory propionic acid.

6. A use according to claim 1, wherein said non-steroidal anti-inflammatory compound is selected from the group consisting of sodium salicylate, acetaminophen, phenacetin, ibuprofen, ketoprofen, indomethacin, flurbiprofen, diclofenac, naproxen, piroxicam, tebufelone, etodolac, nabumetone, tenidap, alcofenac, antipyrine, amimopyrine, dipyrone, animopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, meclofenamic acid, mefenamic acid, niflumic acid, salidifamides, sulindac, suprofen, tolmetin, nabumetone, tiaramide, proquazone, bufexamac, flumizole, tinoridine, timegadine, dapsone, diflunisal, benorylate, fosfosal, fenclofenac,

etodolac, fentiazac, tilomisole, carprofen, fenbufen, oxaprozin, tiaprofenic acid, pirprofen, feprazone, piroxicam, sudoxicam, isoxicam, celecoxib, Vioxx© and tenoxicam.

7. A use according to claim 6, wherein said non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, sodium salicylate, acetaminophen, ibuprofen, ketoprofen, and naproxen.

8. A use according to claim 1, wherein said composition comprises a pharmaceutically acceptable amide of isovaleric acid, and wherein said amide is isovaleramide.

9. A use according to claim 8, wherein said composition comprises isovaleramide and ibuprofen.

10. A use according to claim 8, wherein said composition comprises isovaleramide and aspirin.

11. A use according to claim 8, wherein said composition comprises isovaleramide and acetaminophen.

12. A use according to claim 8, wherein said composition comprises isovaleramide and acetylsalicylic acid

13. A use according to claim 8, wherein said composition comprises isovaleramide and naproxen.

14. A use according to claim 8, wherein said composition comprises isovaleramide and ketoprofen.

15. Use of an extract of Valerianaceae, cramp bark, black haw, or hops in combination with at least one non-steroidal anti-inflammatory compound in the preparation of a pharmaceutical formulation for use in a method of treating acute muscular aches, strains, and sprains which occur from a localized, external insult to a particular muscle or muscle group outside of, or peripheral to, the CNS wherein said extract comprises at least one compound that is hydrolyzed *in vivo* to yield isovaleric acid or isovaleramide.

16. A use according to claim 15, wherein said non-steroidal anti-inflammatory compound is ibuprofen.

17. A use according to claim 15, wherein said non-steroidal anti-inflammatory compound is aspirin.

18. A use according to claim 15, wherein said non-steroidal anti-inflammatory compound is acetaminophen.

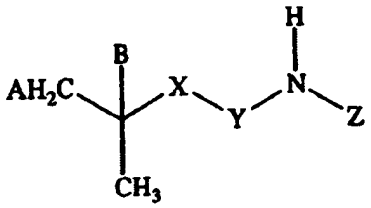
19. A use according to claim 15, wherein said non-steroidal anti-inflammatory compound is acetylsalicylic acid

20. A use according to claim 15, wherein said non-steroidal anti-inflammatory compound is naproxen.

21. A use according to claim 15, wherein said non-steroidal anti-inflammatory compound is ketoprofen.

22. A pharmaceutical composition comprising (a) at least one non-steroidal anti-inflammatory compound, and; (b) at least one compound selected from the group consisting of isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, a

pharmaceutically acceptable amide of isovaleric acid and a compound having the structure:



wherein A = H, CH_3 or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH)-, or $-CH_2O-$,

Y = -CO-, or $-SO_2-$, and

Z = H, CH_2CO_2H, or CH_2CONH_2

and wherein said compound is selected from the group consisting of 2-methyl isovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate,

together with a pharmaceutically acceptable diluent, excipient, or carrier.

23. A composition according to claim 22, wherein said non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, a non-steroidal antiinflammatory acetic acid, a fenamate, an oxicam, and a non-steroidal anti-inflammatory propionic acid.

24. A composition according to claim 22 wherein said non-steroidal anti-inflammatory compound is selected from the group consisting of sodium salicylate, acetaminophen, phenacetin, ibuprofen, ketoprofen, indomethacin, flurbiprofen, diclofenac, naproxen, piroxicam, tebufelone, etodolac, nabumetone, tenidap, alcofenac, antipyrine, amimopyrine, dipyrone, animopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, meclofenamic acid, mefenamic acid, niflumic acid, salidifamides, sulindac, suprofen, tolmetin, nabumetone, tiaramide, proquazone, bufexamac, flumizole, tinoridine, timegadine, dapsone, diflunisal, benorylate, fosfosal, fenclofenac, etodolac, fentiazac, tilomisole, carprofen, fenbufen, oxaprozin, tiaprofenic acid, pirprofen, feprazone, piroxicam, sudoxicam, isoxicam, celecoxib, Vioxx® and tenoxicam.

25. A composition according to claim 22, wherein said non-steroidal anti-inflammatory compound is selected from the group consisting of aspirin, sodium salicylate, acetaminophen, ibuprofen, ketoprofen, and naproxen.

26 A composition according to claim 22, wherein said composition comprises a pharmaceutically acceptable amide of isovaleric acid, and wherein said amide is isovaleramide.

27. A composition according to claim 22, wherein said composition comprises isovaleramide and ibuprofen.

28. A composition according to claim 22, wherein said composition comprises isovaleramide and aspirin.

29. A composition according to claim 22, wherein said composition comprises isovaleramide and acetaminophen.

30. A composition according to claim 22, wherein said composition comprises isovaleramide and acetylsalicylic acid

31. A composition according to claim 22, wherein said composition comprises isovaleramide and naproxen.

32. A composition according to claim 22, wherein said composition comprises isovaleramide and ketoprofen.

33. A pharmaceutical composition comprising an extract of Valerianaceae, cramp bark, black haw, or hops and at least one non-steroidal anti-inflammatory compound, together with a pharmaceutically acceptable diluent, excipient, or carrier.

34. A composition according to claim 33, wherein said non-steroidal anti-inflammatory compound is ibuprofen.

35. A composition according to claim 33, wherein said non-steroidal anti-inflammatory compound is aspirin.

36. A composition according to claim 33, wherein said non-steroidal anti-inflammatory compound is acetaminophen.

37. A composition according to claim 33, wherein said non-steroidal anti-inflammatory compound is acetylsalicylic acid

38. A composition according to claim 33, wherein said non-steroidal anti-inflammatory compound is naproxen.

39. A composition according to claim 33, wherein said non-steroidal anti-inflammatory compound is ketoprofen.

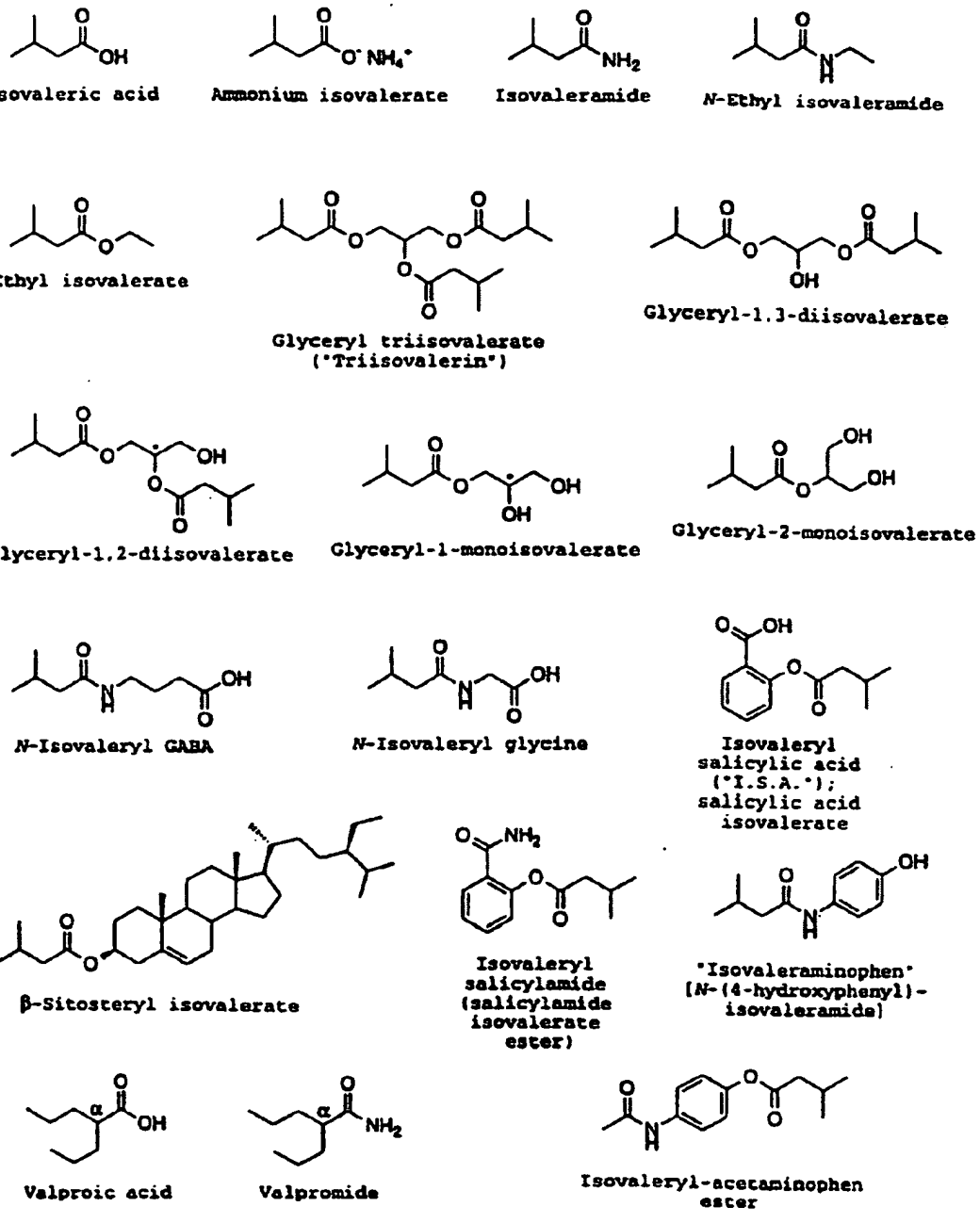
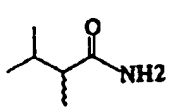
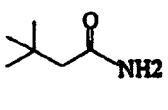

Isovaleric acid
Ammonium isovalerate
Isovaleramide
N-Ethyl isovaleramide
Ethyl isovalerate
Glyceryl triisovalerate ("Triisovalerin")
Glyceryl-1,3-diisovalerate
Glyceryl-1,2-diisovalerate
Glyceryl-1-monoisovalerate
Glyceryl-2-monoisovalerate
N-Isovaleryl GABA
N-Isovaleryl glycine
Isovaleryl salicylic acid ("I.S.A."); salicylic acid isovalerate
β-Sitosteryl isovalerate
Isovaleryl salicylamide (salicylamide isovalerate ester)
"Isovaleraminophen" [N-(4-hydroxyphenyl)-isovaleramide]
Valproic acid
Valpromide
Isovaleryl-acetaminophen ester

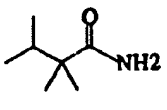
FIG. 1



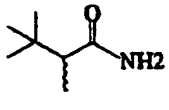
2-methyl isovaleramide



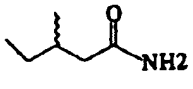
3-methyl isovaleramide



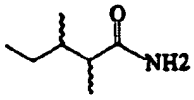
2,2-dimethyl isovaleramide



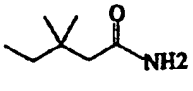
2,3-dimethyl isovaleramide



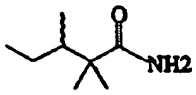
4-methyl isovaleramide



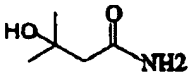
2,4-dimethyl isovaleramide



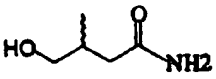
3,4-dimethyl isovaleramide



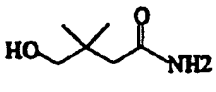
2,2,4-trimethyl isovaleramide



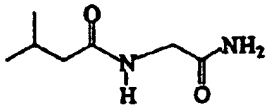
3-hydroxy isovaleramide



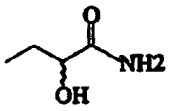
4-hydroxy isovaleramide



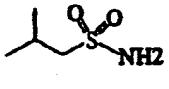
4-hydroxy-3-methyl isovaleramide



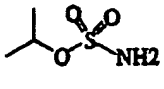
N-(2-acetamido) isovaleramide



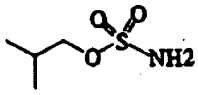
2-hydroxyl isovaleramide



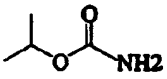
2-methyl-1-propyl sulfonamide



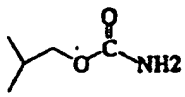
1-methylethyl sulfamate



2-methyl-1-propyl sulfamate



Isopropyl carbamate



Isobutyl carbamate

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/04786

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/78 A61K31/16 A61K31/19 A61K31/60 A61K31/165
//(A61K35/78,31:60),(A61K35/78,31:165),(A61K35/78,31:19),
(A61K31/19,31:165),(A61K31/60,31:19),(A61K31/60,31:165),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 08498 A (ARTMAN LINDA D ;NPS PHARMA INC (US); BALANDRIN MANUEL F (US)) 5 March 1998 see claims ---	1-39
Y	US 3 485 851 A (THIES PETER WILLIBRORD) 23 December 1969 see abstract ---	1-39
Y	DE 22 30 626 A (SCHAETTE ROLAND DR) 10 January 1974 see page 1, line 5-13 ---	15-21, 33-39

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 1999	06/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 99/04786

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (A61K31/19,31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAZELHOFF B ET AL: "ANTISPASMODIC EFFECTS OF VALERIANA COMPOUNDS: AN IN-VIVO AND IN -VITRO STUDY ON THE GUINEA-PIG ILEUM" ARCHIVES INTERNATIONALES PHARMACODYNAMIE ET DE THERAPIE, vol. 257, no. 2, 1 May 1982, pages 274-287, XP002049842 see abstract ---	15-21, 33-39
Y	BALANSARD G ET AL: "CRITERES DE CHOIX D'UN EXTRAIT DE VIBURNUM, VIBURNUM PRUNIFOLIUM L.EN FONCTION DE SES ACTIONS TONIVEINEUSE ET SPASMOLYTIQUE" PLANTES MEDICINALES ET PHYTOTHERAPIE, vol. 17, no. 3, 1 July 1983, pages 123-132, XP002049844 see abstract ---	15-21, 33-39
	-/--	

[X] Further documents are listed in the continuation of box C.

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* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/04786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	B ZANGER-BEAUQUESNE ET AL: "CANNABINACEES" PLANTES MEDICINALES DES REGIONS TEMPEREES, pages 78, 363-365, XP002049849 BEZANGER-BEAUQUESNE L;PINKAS M; TORCK M; TROTIN F see the whole document	15-21, 33-39
Y	WAGNER H ET AL: "UEBER DIE SPASMOLYTISCHE WIRKUNG DES BALDRIANS. ON THE SPASMOLYTIC ACTIVITY OF VALERIANA EXTRACTS" PLANTA MEDICA, vol. 37, no. 1, 1 September 1979, pages 84-86, XP002049846 see the whole document	15-21, 33-39
Y	MORAZZONI P ET AL: "VALERIANA OFFICINALIS: TRADITIONAL USE AND RECENT EVALUATION OF ACTIVITY" FITOTERAPIA, vol. 66, no. 2, 1 January 1995, pages 99-112, XP002049843 see abstract	15-21, 33-39
Y	WO 94 28888 A (NPS PHARMA INC ;BALANDRIN MANUEL F (US); WAGENEN BRADFORD C VAN (U) 22 December 1994 see claims 1-13	1-14, 22-31
Y	JAMES E.F. REYNOLDS: "MARTINDALE The Extra Pharmacolpoeia" 1993 , THE PHARMACEUTICAL PRESS , LONDON XP002106692 See page 1-2, esp. p. 1, right column, 1st paragraph under "Uses and Administraton"	1-39
Y	DATABASE EPODOC European Patent Office CN1160512, 1 October 1997 XP002106693 see abstract & CN 1 160 513 A (CHENGDU HUAFUNING PHARMACEUTIC) 1 October 1997	15-21, 33-39
Y	DATABASE EPODOC European Patent Office CN1152416, 25 June 1997 XP002106694 see abstract & CN 1 152 416 A (SHAO DONGYING) 25 June 1997	15-21, 33-39

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

h ational Application No
PCT/US 99/04786

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 3485851 A	23-12-1969	DE 1617555 A	01-04-1971
		DK 115651 B	27-10-1969
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		AU 701360 B	28-01-1999
		AU 7100694 A	03-01-1995
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		IL 109982 A	24-09-1998
		JP 9501908 T	25-02-1997
		US 5763494 A	09-06-1998

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	Babish *et al.*
Application No.: 10/774,048	)	Group Art Unit: 1655
Filing Date:	)	February 4, 2004
Examiner:	)	Michael V. Meller
Title:	)	COMPLEX MIXTURES EXHIBITING SELECTIVE INHIBITION OF CYCLOOXYGENASE-2
Atty. Docket No.:	)	068911-0062

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT and REQUEST FOR RECONSIDERATION UNDER 37 C.F.R § 1.111

Responsive to the Office Action mailed November 14, 2005 (the "Office Action"), entry of the following amendments, and consideration of the following remarks are respectfully requested. The Response is now due February 14, 2005.

Amendments to the claims begin on page 2.

Remarks begin on page 6.

AMENDMENT TO THE CLAIMS

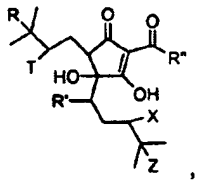
A listing of the claims presented in this patent application appears below. This listing replaces all prior versions and listing of claims in this patent application.

Please amend the claims as shown below:

1. (Original) A composition comprising a fraction isolated or derived from hops and a non-aspirin, non-steroidal anti-inflammatory compound.

2. (Original) The composition of claim 1, wherein the fraction isolated or derived from hops is selected from the group consisting of alpha acids, isoalpha acids, reduced isoalpha acids, tetra-hydroisoalpha acids, hexa-hydroisoalpha acids, beta acids, and spent hops.

3. (Original) The composition of claim 1, wherein the said fraction isolated or derived from hops comprises a compound of a supragenus having the formula:



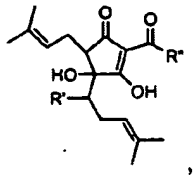
(Supragenus),

wherein R' is selected from the group consisting of carbonyl, hydroxyl, OR, and OCOR, wherein R is alkyl;

wherein R" is selected from the group consisting of $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$;

and wherein R, T, X, and Z are independently selected from the group consisting of H, F, Cl, Br, I, and π orbital, with the proviso that if one of R, T, X, or Z is a π orbital, then the adjacent R, T, X, or Z is also a π orbital, thereby forming a double bond.

4. (Original) The composition of claim 1, wherein said fraction isolated or derived from hops comprises a compound of Genus A having the formula:

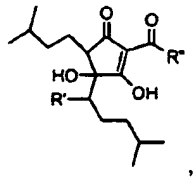


(Genus A),

wherein R' is selected from the group consisting of carbonyl, hydroxyl, OR, and OCOR, wherein R is alkyl;

and wherein R" is selected from the group consisting of $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$.

5. (Original) The composition of claim 1, wherein the fraction isolated or derived from hops comprises a compound of Genus B having the formula:



(Genus B),

wherein R' is selected from the group consisting of carbonyl, hydroxyl, OR, and OCOR, wherein R is alkyl;

and wherein R" is selected from the group consisting of $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, and $CH(CH_3)CH_2CH_3$.

6. (Original) The composition of claim 1, wherein said fraction isolated or derived from hops comprises a compound selected from the group consisting of humulone, cohumulone, adhumulone, isohumulone, isocohumulone, isoadhumulone, dihydro-isohumulone, dihydro-isocohumulone, dihydro-adhumulone, tetrahydro-isohumulone, tetrahydro-isocohumulone, tetrahydro-adhumulone, hexahydro-isohumulone, hexahydro-isocohumulone, and hexahydro-adhumulone.

7. (Original) The composition of claim 1, wherein the composition comprises about 0.5 to 10000 mg of said fraction isolated or derived from hops.

8. (Original) The composition of claim 7, wherein the composition comprises about 50 to 7500 mg of the fraction isolated or derived from hops.

9. (Original) The composition of claim 1, wherein the composition comprises about 0.001 to 10 weight percent of the fraction isolated or derived from hops.

10. (Original) The composition of claim 9, wherein the composition comprises about 0.1 to 1 weight percent of the fraction isolated or derived from hops.

11. (Original) The composition of claim 1, wherein the non-aspirin, nonsteroidal anti-inflammatory compound is selected from the group consisting of salicylic acid, methyl salicylate, difulunisal, salsalate, olsalazine, sulfasalazine, acetanilide, acetaminophen, phenacetin, mefenamic acid, sodium meclofenamate, tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, sodium daproxen, fenoprofen, ketoprofen, flurbioprofen, oxaprozin, piroxicam, meloxicam, tenoxicam, ampiroxicam, droxicam, pivoxicam, phenylbutazone, oxyphenbutazone, anitpyrine, aminopyrine, dipyrone, celecoxib, rofecoxib, nabumetone, apazone, nimensulide, indomethacin, sulindac, and etodolac.

12. (Currently Amended) The composition of claim 1, wherein the non-aspirin, nonsteroidal anti-inflammatory compound is selected from the group consisting of salicylic acid, methyl salicylate, ibuprofen, naproxen, sodium daproxen, fenoprofen, ketoprofen, flurbioprofen, and oxaprozin.

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13. (Original) The composition of claim 1, wherein the composition further comprises a pharmaceutically acceptable carrier.

14. (Original) The composition of claim 1, wherein the composition is formulated for administration orally, topically, parenterally, or rectally.

15. (Original) A composition comprising a reduced isoalpha acid isolated from hops and a non-steroidal anti-inflammatory compound.

16. (Original) The composition of claim 15, wherein the reduced isoalpha acid is selected from dihydro-isohumulone, dihydro-isocohumulone, and dihydro-adhumulone.

17-36 (Canceled).

REMARKS

Claims 1-16 are pending in the subject application. Applicant confirms the election with traverse of group I claims 1-16 in response to the restriction requirement and cancel claims 17-36 without prejudice or disclaimer. Applicant confirms the election with traverse of naproxen as a species selection. The amendment to claim 12 is made merely to correct a typographical error; no new matter is added to the claims.

1. The Amended Claims are patentable over the Art Cited Under 35 U.S.C. § 103(a).

1.1. The Rejection of Claims 1-16 under 35 U.S.C. § 103(a) over WO 99/44623

Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentably obvious over WO 99/44623 ("WO") (abstract; page 4, lines 3-15; page 6, lines 6-20). Examiner asserts that WO teaches that hops and naproxen can be in the same composition, and that it would have been obvious to select them from a list in WO list because they are both noted to be used in a single composition to treat inflammation. Applicant respectfully disagrees that the combination of components of the present invention would have been obvious to one skilled in the art.

In the present invention, the addition of hops extracts to naproxen or other non-steroidal anti-inflammatory drugs (NSAIDs) not only yields an enhanced anti-inflammatory effect over NSAIDs alone, but the combination also reduces the gastropathy of the NSAID. WO only suggests that the combination a NSAID with hops that have been treated to specifically produce isovaleric or isovaleramide may decrease inflammation and muscle tone associated with muscle pain.

1.1.1. WO suggests Isovaleric acid and NSAIDs reduce muscle tone and inflammation

WO recites "there has been provided a use of an extract of . . . hops in combination with at least one non-steroidal anti-inflammatory compound . . . for use in a method of treating acute muscular aches, strains, and sprains," (page 4, lines 3-15). The key characteristic WO emphasizes of the hops extract is that it is "hydrolyzed *in vivo* to yield isovaleric acid or isovaleramide (page 26, claim 15), which is purported to decrease muscle tone associated with muscle pain: "the dosages of the muscle-tone decreasing agents and the NSAID compounds described herein . . ." (page 18, lines 24-25).

WO does not discuss experiments involving hops, but suggests that results of experiments involving valerian extract would produce similar results if practiced with hops. In the description regarding Valerian extracts which WO uses as an alternative for hops, WO recites "Valerian

extracts and valerian-related compounds can be administered in combination with at least one NSAID compound, such as ibuprofen, *in vivo*, to reduce acute muscle pain by decreasing muscle tone and inflammation." (page 6, lines 28-30). Throughout the application, WO suggests that the expected results from the combination of isovaleric acid or isovaleramide yielded from hops extract with a NSAID such as naproxen would be an increased anti-inflammatory response and decreased muscle tone to increase relief of muscle pain.

1.1.2. The present invention teaches hops extracts with NSAIDs to reduce NSAIDs-gastropathic side effects

The combination of hops extracts with naproxen for the use in the present invention is not obvious over WO, because unexpected results were obtained. The current invention's combination of hops extracts with naproxen not only yields a greater anti-inflammatory response than hops extracts or NSAIDs alone, but also the hops extracts "prevent or attenuate gastropathy, and particularly but not exclusively that caused by non-steroidal anti-inflammatory drugs." (para 2; lines 5-8).

NSAIDs inhibit the production of cyclooxygenase (COX) which catalyzes the rate limiting step in the production of prostraglandins (PGs) which cause inflammatory responses. COXs are of two types: COX-1, which affects PGs that maintain physiological functions such as regulation of gastric mucosa, renal blood flow and platelet aggregation, and COX-2 which affects PGs that mainly increase inflammation. NSAIDs alone inhibit both COX-1 and COX-2, which leads to gastric irritation and potentially gastric bleeding and/or kidney damage. (para. 5-7; para.15, lines 1-2). The present invention has found "that chemically induced ulceration, produced by analgesic and/or anti-inflammatory drugs such as ibuprofen, aspirin and indomethacin, or other chemical agents, is significantly reduced when these drugs are administered in combination with hop derivatives." (para. 42). A reduction in ulceration from a hops extract and NSAID combination is unexpected from the teachings of WO.

When hops extracts are combined with NSAIDs, a decreased inhibition of PGs in gastric mucosal cells is found compared to the use of NSAIDs alone. (Examples 5 and 6). While also yielding a reduction in inflammation, the addition of hops extracts to NSAIDs in the present invention yields the unexpected result of decreased gastric ulceration caused by NSAIDs because the compounds leading to formation of gastric mucosa are inhibited less. The effect of hops derivatives with naproxen would be similar to the results obtained with ibuprofen or aspirin in

examples 5 and 6, because, as is known to persons of skill in the art, NSAIDs work by inhibiting COX-1, which catalyzes the reactions for PGs which maintain physiological functions. Decreased inhibition of PGs that maintain physiological functions would be directly related to the inhibition by hops of COX-1, whether the inhibition of COX-1 was caused by ibuprofen, aspirin, naproxen, or any other NSAID. Because hops derivatives prevent the inhibition of COX-1, a decrease in PGs that maintain physiological function is also prevented, regardless of the particular NSAID targeting COX-I.

1.1.3. The present invention teaches combinations of compounds not obvious over WO

The present invention further is not obvious over WO because WO only teaches combinations of NSAIDs with hops extracts that hydrolyze *in vivo* to produce isovaleric acid or isovaleramide, whereas the present invention teaches combinations of NSAIDs with hop extracts or with extracts containing compounds of the Supragenus structure (claim 3) or of the Genus A or B structure (claims 4-5), all of which extracts that do not necessarily hydrolyze to yield isovaleric acid or isovaleramide. Further, WO does not teach or suggest hops extracts containing compounds having the formulas of Supragenus (claim 3), Genus A or B (claims 4 – 5).

Applicants respectfully submit that the foregoing amendments and remarks have fully addressed the Examiner's rejection under 35 U.S.C. § 103 and, therefore, request its removal.

1.2. The Rejection of Claims 1-16 Based on JP 406312924 (abstract) or JP 04202138 (abstract)

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 406312924 (abstract) or JP 04202138 (abstract) taken with Sunshine et al. (US patent No. 4780463) or CA 2175091 (abstract).

Examiner asserts that JP 406312924 (abstract) or JP 04202138 (abstract) both teach hops extracts used to treat inflammation. Examiner asserts that both Sunshine et al. (US patent No. 4780463) and CA 2175091 (abstract) teach the use of naproxen to treat inflammation.

As described above, the present invention teaches the use of hops extract with naproxen or other NSAIDs to reduce the physiological problems, such as gastropathy, caused by NSAIDs' inhibition of COX-1. This use of hops is not used to treat inflammation, but rather to extinguish or ameliorate the gastropathic side effects of naproxen or other NSAIDs. The results of the present

invention which are discussed above in section 1.1, are not obvious over the cited prior art, which only suggest a combination of hops with NSAIDs reduces inflammation, but not that the combination reduces the side effects caused by NSAIDs' inhibition of COX-1.

For the foregoing reasons, applicants aver that the claimed invention is not obvious over the cited prior art. Accordingly, it is respectfully requested that the rejection of claims 1-16 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Accordingly, it is respectfully requested that the rejection of claims 1-8 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

It is submitted that the amended claims are patentable over the teachings of the prior art relied upon by the Examiner. Accordingly, favorable reconsideration of the claims is requested in light of the preceding amendments and remarks. Allowance of the claims is courteously solicited.

If there are any outstanding issues that might be resolved by an interview or an Examiner's amendment, the Examiner is requested to call Applicant's attorney at the telephone number shown below.

Pursuant to 37 C.F.R. § 1.136(a)(2), the Examiner is authorized to charge any fee under 37 C.F.R. § 1.17 applicable in this instant, as well as in future communications, to Deposit Account 50-1133. Furthermore, such authorization should be treated in any concurrent or future reply requiring a petition for an extension of time under Section 1.136 for its timely submission, as constructively incorporating a petition for extension of time for the appropriate length of time pursuant 37 C.F.R. § 1.136(a)(3) regardless of whether a separate petition is included.

Respectfully submitted,
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_____
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